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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/584,216	05/31/2000	Sarah Ferber	21415-501	2453

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EXAMINER
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ART UNIT	PAPER NUMBER
1632	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
09/584,216	Ferber, S.
Examiner	**Art Unit**
Joseph Woitach	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) [X] Responsive to communication(s) filed on *Dec 18, 2002*.

2a) [X] This action is **FINAL**. 2b) [ ] This action is non-final.

3) [ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) [X] Claim(s) *1, 10-13, 15, 29-31, and 33-42* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) [X] Claim(s) *37-42* is/are allowed.

6) [X] Claim(s) *1, 10-13, 15, 29-31, and 33-36* is/are rejected.

7) [ ] Claim(s) _____ is/are objected to.

8) [ ] Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) [ ] The specification is objected to by the Examiner.

10) [X] The drawing(s) filed on *May 31, 2000* is/are a) [X] accepted or b) [ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) [ ] The proposed drawing correction filed on _____ is: a) [ ] approved b) [ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) [ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) [ ] All b) [ ] Some* c) [ ] None of:

1. [ ] Certified copies of the priority documents have been received.
2. [ ] Certified copies of the priority documents have been received in Application No. _____.
3. [ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) [X] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) [ ] The translation of the foreign language provisional application has been received.

15) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [ ] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) [ ] Interview Summary (PTO-413) Paper No(s). _____
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [ ] Other:

DETAILED ACTION

This application, filed May 31, 2000, claims benefit to provisional applications 60/137,143, filed June 1, 1999, and 60/198,532, filed April 19, 2000.

Applicant's amendment filed December 18, 2002, paper number 15, has been received and entered. The specification has been amended. Claims 2, 9, 16-17, 24, 26-28 and 32 have been canceled. Claims 1, 10-13, 15, 29 and 31 have been amended. Claims 33- 42 have been added. Claims 1, 10-13, 15, 29, 31 and 33- 42 are pending and currently under examination as they are drawn to the delivery of a nucleic acid encoding PDX.

Specification

The amendments to the specification to include SEQ ID NOs for each of the sequences disclosed has obviated the basis of the objection. This application complies with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825.

Claim Objections

Claims 1 and 29 objected to because the claims are not drawn to the elected invention for the delivery of a polynucleotide is withdrawn.

Amendments to the claims has obviated the basis of the objection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 10-13, 15, 29, 31 stand rejected and newly added claims 33-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing insulin, somatostatin, glucagon and prohormone convertase 1/3 gene expression in the liver of mammals comprising administering a recombinant adenovirus wherein said adenoviral vector comprises a cytomegalovirus (CMV) promoter operably linked to a nucleic acid encoding a pancreatic and duodenal homobox 1 (PDX-1) polypeptide in an amount effective enough to obtain PDX expression in the liver of said mammal, does not reasonably provide enablement for use of other delivery vehicles, inducing any and all pancreatic hormones, or providing a therapeutic affect to a subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants summarize the amendments to the claims and note that the claims are not directed to other delivery vehicles (pages 11-12). Specifically, it is noted that the instant claims are directed to the use of an adenovirus vector having a CMV promoter operably linked to a polynucleotide sequence encoding PDX-1 and Applicants argue that given the guidance in the

specification one of skill in the art could practice the instantly claimed invention (pages 12-13). Further, Applicants note that these embodiments have been indicated as enabled by the Examiner in the basis of the rejection (page 13). See Applicant's amendment, pages 11-13. Applicants' arguments have been fully considered and found persuasive in part.

Initially, Examiner would agree that an adenovirus vector having a CMV promoter operably linked to a polynucleotide sequence encoding PDX-1 comprises the critical features of a vector required to practice the claimed methods, and that the methods are enabled for use of more than the single adenoviral vector AdCMVPDX-1. Further, the ability to affect each of the insulin, somatostatin and glucagon genes in the liver cell would be inherent if adequate amounts of the PDX-1 protein was produced by the vector. Additionally, the methods restricted to the administration of an adenovirus vector is by contacting a liver cell (claims 37-37) would be fully enabled because the vector is delivered directly to the liver cell.

However, with respect to the method practiced *in vivo*, only the use of adenoviral particles comprising the adenovirus vector comprising a CMV promoter operably linked to a polynucleotide sequence encoding PDX-1 would be enabled for the delivery by various routes of administration. Alternatively, delivery of a adenovirus vector to a liver cell *in vivo* can only be accomplished by the direct injection of the vector to the liver. As noted in the previous office action, in light of the working example in the present specification it appears that the delivery of an adenovirus and the level of expression of PDX afforded by the CMV promoter results in adequate levels of PDX necessary to affect gene expression in the liver. More specifically, the

instant specification teaches that the use of AdCMVPDX can effectively increase the expression of several pancreatic genes in the liver. In the systemic delivery of adenovirus the predominant site of uptake of the adenovirus is in the liver. Therefore, the use of an adenovirus for the delivery of an adenovirus vector would be enabled for systemic delivery.

With respect to the use of adenovirus vector itself, the specification teaches that a 'vector' is 'a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked' (emphasis added, page 13, lines 22-23), and thus, an adenovirus vector is limited to simply the polynucleotide sequences. The polynucleotide of an adenovirus themselves lack the ability to specifically target the liver and it is only in the context of the polynucleotide in a adenoviral particle which would be enabled for any route of delivery. As noted by Anderson at the time of filing "major deficiencies still exist including poor delivery system, both viral and no-viral, and poor gene expression after genes are delivered" (p. 30). Examiner would agree that once the polynucleotide is delivered to the liver cell the expression of an adenoviral vector which contains the PDX-1 gene operably linked to the CMV promoter can increase the expression of several pancreatic hormones in the liver. Thus, the only enabled route of delivery for the polynucleotide alone would be through the direct administration of the adenovirus vector to the cells of the liver. In this case the specification lacks the necessary and specific guidance for the use and delivery of any other vector/polynucleotide, and thus, is subject to the same obstacles recognized by others skilled in the art.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed and the rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 31 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Initially, amendments to the claims has obviated the basis of each of the previous specific rejections of record.

With respect to claim 31, the claim is vague and unclear in the recitation of 'in amount effective to induce pancreatic hormone expression in the liver cell' because the polynucleotide does not induce the expression in the cell, it is the PDX-1 protein encoded and produced by the polynucleotide. The claim is confusing because it is unclear how this limitation applies to a polynucleotide which does not have itself this activity. Further, if it is the property of the encoded polypeptide, the metes and bounds of the claim are indefinite because the effective amount of a polynucleotide would be dependent the ability of the polynucleotide to express adequate amounts of the polypeptide which can not be assessed nor is it set forth in the claim.

The recitation is vague and unclear because it appears to describe an inherent property of the PDX-1 polypeptide without further limiting the polynucleotide or polypeptide encoded therefrom, and only provides one potential use for the polynucleotide encoding PDX-1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 31 stands rejected under 35 U.S.C. 102(b) as being anticipated by Milewski *et al.*

Applicants note the amendments to the claim and argue that Milewski *et al.* do not teach 'an amount effective to induce pancreatic hormone expression in a liver cell', thus Milewski *et al.* does not teach every limitation encompassed by the claim. Additionally, with respect to newly added claim 42, Applicants argue that Milewski *et al.* does not teach an adenovirus vector. See Applicant's amendment, page 14. Applicant's arguments have been fully considered but not found persuasive.

Initially, Examiner agrees that Milewski *et al.* does not anticipate claim 42. However, as noted above in the rejection made under 35 USC 112, second paragraph, the limitation of 'an amount effective to induce pancreatic hormone expression in a liver cell' describes an inherent

property of PDX-1 protein and provides only an intended use of the polynucleotide. Milewski *et al.* teach several vectors which comprise the sequences which encode zebrafish and mouse PDX wherein when the vector is administered to a cell, PDX is expressed and the increased activity of PDX activity in said cell is measured by promoter reporting construct (results summarized in Figure 8, page 1448). Examiner agrees Milewski *et al.* do not teach 'an amount effective to induce pancreatic hormone expression in a liver cell' however because the vectors described by Milewski *et al.* meet the structural limitation of encoding a PDX-1 polypeptide and demonstrate that the vector is capable of expression in cells in culture the vectors of Milewski *et al.* would anticipate the vector as instantly claimed. Where, as here, the claimed and prior art products are identical or substantially identical, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. Whether the rejection is based on "inherency" under 35 USC 102, or "*prima facie* obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Thus, the vectors containing the polynucleotide sequences which encode PDX meet the limitations set forth in the claim.

Claim 31 stands rejected under 35 U.S.C. 102(b) as being anticipated by Marshak *et al.*

Applicants note the amendments to the claim and argue that Marshak *et al.* do not teach 'an amount effective to induce pancreatic hormone expression in a liver cell', thus Marshak *et al.* does not teach every limitation encompassed by the claim. Additionally, with respect to newly added claim 42, Applicants argue that Marshak *et al.* does not teach an adenovirus vector. See Applicant's amendment, page 15. Applicant's arguments have been fully considered but not found persuasive.

Examiner agrees that Marshak *et al.* does not anticipate claim 42. However, as noted above in the rejection made under 35 USC 112, second paragraph, the limitation of 'an amount effective to induce pancreatic hormone expression in a liver cell' describes an inherent property of PDX-1 protein and provides only an intended use of the polynucleotide. Marshak *et al.* teach a polynucleotide sequence which encodes PDX (summarized in abstract). Examiner agrees Marshak *et al.* do not teach 'an amount effective to induce pancreatic hormone expression in a liver cell' however because the vectors described by Marshak *et al.* meet the structural limitation of encoding a PDX-1 polypeptide and demonstrate that the vector is capable of expression in cells in culture the vectors of Marshak *et al.* would anticipate the vector as instantly claimed. Where, as here, the claimed and prior art products are identical or substantially identical, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. Whether the rejection is based on "inherency" under 35 USC 102, or "*prima facie* obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture

products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Thus, the polynucleotide sequences which encode PDX which can be delivered to cells meet each of the limitations set forth in the claim.

Conclusion

Claims 37-42 are allowed. Claims 1, 10-13, 15, 29 and 33- 36 are free of the art of record, however they are subject to other rejections.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however,

will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist Pauline Farrier whose telephone number is (703)305-3550.

Deborah Crouch

Joseph T. Woitach

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630